EXHIBIT A

Abstracts search

« Back to Abstract Listing by Author

Board Number: P-13
Title: Potential Impurities Generated from Ethylene Oxide Sterilization Process

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Ethylene oxide (EtO) treatment is a common process for the sterilization of the packaging components. The technology involves exposure of the packaging components to ethylene oxide gas followed by an aeration process. It has been found that the residual ethylene oxide if trapped in the container/closure system could react with the active drug substance (mainly in solution formulations) and result in the formation of unexpected impurity(s). Such an EtO-drug substance impurity has been observed in a commercial product. Particularly, if the drug substance contains some nucleophilic functional groups or moieties, such as acid anions, alkoxide anions and any neutral molecule that has an unshared electron pair, a SN_2 nucleophilic reaction of the drug substance with the ethylene oxide will occur. The EtO-drug substance impurity with a mass increase of 44 ($-CH_2CH_2O^-$) will be formed. To verify the origin of these impurities (interaction between the drug substance and ethylene oxide or its residuals), a solution of the drug substance may be designed to react with each of the chemicals such as carbon dioxide, ethylene oxide, formaldehyde, ethylene chlorohydrin, ethylene glycol, and isopropyl alcohol under the stressed condition (70°C for couple of hours). To avoid the formation of these impurities, the aeration time of the packaging components should be evaluated to control the ethylene oxide residual level in the container/closure system. Alternatively, gamma irradiation or heat sterilization rather than EtO sterilization could be considered.

Category: P. Validation, Testing, Standardization, and Quality Assurance